**PCT** WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07J 1/00, A61K 31/565 — A1

(11) International Publication Number: **WO 00/23460**

(43) International Publication Date: 27 April 2000 (27.04.00)

(21) International Application Number: PCT/EP99/07768

(22) International Filing Date: 11 October 1999 (11.10.99)

(30) Priority Data:
98203460.5 16 October 1998 (16.10.98) EP

(71) Applicant *(for all designated States except US)*: AKZO NOBEL N.V. [NL/NL]; Velperweg 76, NL-6824 BM Arnhem (NL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: KIRCHHOLTES, Peter, Huub, Gerard, Maria [NL/NL]; Gewandeweg 58, NL-5345 HN Oss (NL). SAS, Gerard, Arnoud, Jozef, Maria, Theresia [NL/NL]; Vlas en Graan 79, NL-5461 KL Veghel (NL).

(74) Agent: HERMANS, Frans; P.O. Box 20, NL-5340 BH Oss (NL).

(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published**
*With international search report.*

(54) Title: HIGH PURITY COMPOSITION COMPRISING (7α,17α)- 17-HYDROXY- 7-METHYL- 19-NOR-17-PREGN-5(10)-EN-20-YN-3-ONE

(57) Abstract

The invention pertains to a process for the preparation of a high purity composition of (7α,17α)- 17-hydroxy- 7-methyl- 19-nor-17-pregn- 5(10)-en-20-yn-3-one. The process provides for a composition with less than 0.5 % of (7α,17α)- 17-hydroxy- 7-methyl- 19-nor-17-pregn- 4-en-20-yn- 3-one. This composition can be used as a source for the preparation of stable pharmaceutical dosage units.

*FOR THE PURPOSES OF INFORMATION ONLY*

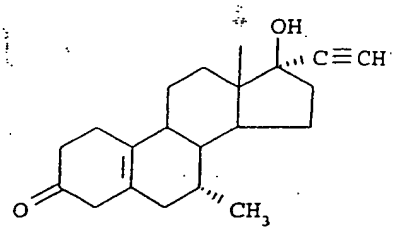
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | | | TR | Turkey |
| BG | Bulgaria | HU | Hungary | ML | Mali | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MN | Mongolia | UA | Ukraine |
| BR | Brazil | IL | Israel | MR | Mauritania | UG | Uganda |
| BY | Belarus | IS | Iceland | MW | Malawi | US | United States of America |
| CA | Canada | IT | Italy | MX | Mexico | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NE | Niger | VN | Viet Nam |
| CG | Congo | KE | Kenya | NL | Netherlands | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NO | Norway | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | NZ | New Zealand | | |
| CM | Cameroon | | | PL | Poland | | |
| CN | China | KR | Republic of Korea | PT | Portugal | | |
| CU | Cuba | KZ | Kazakstan | RO | Romania | | |
| CZ | Czech Republic | LC | Saint Lucia | RU | Russian Federation | | |
| DE | Germany | LI | Liechtenstein | SD | Sudan | | |
| DK | Denmark | LK | Sri Lanka | SE | Sweden | | |
| EE | Estonia | LR | Liberia | SG | Singapore | | |

# High purity composition comprising (7α,17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one

The invention relates to a high purity composition comprising (7α,17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, a method for the preparation of this compound for use in the pharmaceutical composition as well as a pharmaceutical composition prepared by admixing a pharmaceutically suitable carrier and the high purity composition.

The compound (7α,17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one (Tibolone) having the structural formula 1:




Formula 1

is known, for example from US 3,340,279 and US Patent 4,701,450. The method described in these patents leads to a compound having combined oestrogenic, progestagenic and androgenic characteristics. This compound is used in medicaments having gonadomimetic, ovulation-inhibiting or immuno-modulating action.

Compositions comprising Tibolone and a pharmaceutically acceptable solid carrier have been described in EP 389 035, which disclosure is incorporated herein by reference. Tablets are available on the market under the name of Livial®.

The known tablets can be stable stored very well for, typically, 2 years at ambient temperature. A sufficiently humid atmosphere (e.g. 50 - 70 % relative humidity) makes for a better storage stability than a relatively dry atmosphere (e.g. 45% relative humidity or below that).

A problem in the preparation of pharmaceutical dosage units is that during the preparation the relative amount of impurities may increase. In particular, the amount of one of the impurities which is already present in the bulk preparation i.e. (7α,17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one (Org OM38) tends to increase during the process of making pharmaceutical dosage units. It is furthermore known that the amounts of Org OM38 in compositions comprising Tibolone increase upon storage.

The end of shelf life specification with respect to the amount of Org OM38 formed during storage is 5%. A minimum acceptable shelf life period for these dosage units is 1 year. It is an object of the present invention to improve upon the storage stability i.e. to enhance the shelf-live of the dosage units.

The customary amount of Tibolone in the known dosage unit is 2.5 mg in tablets or capsules of 100 mg, i.e. 2.5%. For the sake of providing therapies better tailored to the individual woman's needs, it is desired to provide dosage units having a lower amount.

However, adaptation of a known formulation by simply including a lower amount of Tibolone further decreases the stability of the dosage unit substantially. E.g., if a 2.5 mg Tibolone dosage unit has a shelf-life of, e.g., 2-3 years at room temperature, the same unit upon lowering the amount of Tibolone to e.g. 0.3 mg can only be kept at 4°C for a period of 6-12 months. Such a lower stability is unacceptable in daily practice. It is a further object of the invention to provide dosage forms having a lower content of Tibolone (which are more prone to stability problems than regular dosage forms) and that can be suitably kept for a prolonged period of time.

One of the possibilities to keep the amount of Org OM-38 below a desired level also after a prolonged storage time is to limit the amount initially present in the bulk preparation. Thus, there is a need to synthesize high purity Tibolone batches with a low contamination content of Org OM-38. It is an object of the present invention to provide for such high purity batches of Tibolone.

During the last step of the synthesis of Tibolone a solution of (7α,17α)-3,3-dimethoxy-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one in a mixture of pyridine and ethanol is mixed with a solution of oxalic acid in water and the mixture is stirred for 3 hours at approximately 30 °C. The solution is then poured out in a mixture of pyridine and water and the resulting suspension is filtered. The crystals are washed with a mixture of water and pyridine and subsequently, the crystals are dried under

vacuum at 40 °C to give (7α,17α)-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one (see also van Vliet et al (1986), Recl.Trav.Chim.Pays-Bas *105*, 111-115).

As this compound has a lower stability than the corresponding (7α,17α)-17-hydroxy-7-methyl-19-nor-pregn-4-en-20-yn-3-one there is always formed a small percentage of the latter compound via acid catalyzed isomerisation. Furthermore, this isomerisation takes place at higher temperature and upon long term storage of the crystals

Unexpectedly, it now has been found that the rate of formation of Org OM38 during drying and storage in a specific batch can be decreased if crystals of Tibolone are washed with water and are allowed to age for at least 24 hours in the presence of water. Thus, the Tibolone is left for at least 24 hours under wet conditions. Preferentially the crystals are left under these conditions for a period of at least 3 days. There is no limit to a maximum period but a period of 3-6 days is best suited. The aging temperature preferentially is room temperature.

Thus according to the procedure of the present invention highly pure Tibolone with a low Org OM38 impurity is obtained by including a delay of several days before drying. The procedure reliably results in batches of Tibolone having a low Org OM38 content. A further advantage is that these batches have an excellent stability. Furthermore, these batches do not form additional amounts of the latter compound upon heating or long term storage.

The crystal formation procedure of the present invention can perfectly well be combined with the last step of the Tibolone synthesis wherein (7α,17α)-3,3-dimethoxy-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one in a mixture of pyridine and ethanol is mixed with a solution of oxalic acid in water. In general, this reaction proceeds under mild acidic conditions in the presence of an organic solvent and water within a pH range of 5-3, preferentially 3.5-4.5. The acid preferentially is a weak organic acid having a pKa value in the range 1-5 such as citric acid, malonic acid, oxalic acid, dichloroacetic acid and acetic acid, optionally buffered with a base such as pyridine. As organic solvent e.g. ethanol, methanol, acetone, 2-propanol or tetrahydrofuran can be used. The solution is then poured out in water, which is made slightly alkaline by addition e.g. of a low amount of pyridine. After filtering the suspension the crystals are washed with a mixture of water made slightly alkaline by e.g. pyridine. Before drying the crystals are left wet for at least 24 hours.

Inclusion of the crystal aging step according to the invention results in bulk Tibolone batches with a low Org OM38 content. Routinely, batches are obtained with an Org OM38 content of less than 0.5%. Often even batches with less than 0.25% or even 0.1% of Org OM38 are obtained. Thus high purity compositions with Tibolone having less than 0.5% of Org OM38, preferably 0.25%, more preferably 0.10% of Org OM38 form part of the present invention. The amount of Org OM38 is calculated as the percentage (w/w) of the total amount of the bulk substance including some minor impurities. The amount of Tibolone usually is more than 98%.

The batches of these high purity Tibolone compositions with their low initial Org OM38 content are perfectly well suited to be used as a source for the preparations of pharmaceutical formulations. This guarantees a formulation with a low initial Org OM38 content and improves therefore its storage properties. Pharmaceutical preparations prepared with high purity Tibolone usually result in preparations with less than 1% of Org OM38, often even less than 0.7% of Org OM38 and these preparations are less prone to increase in Org OM38 content during storage.

As indicated before the amount of Org OM38 in a dosage form also depends upon the concentration of the active substance, the amount of impurity being higher as the amount of Tibolone in the dosage unit decreases. Therefore, using high purity Tibolone as the active substance, dosage units can now been prepared with a lower amount of Tibolone and still having an acceptable shelf life. Thus, the invention also relates to pharmaceutical dosage units, which can be prepared by admixture of a pharmaceutically suitable solid carrier and the high purity composition of the present invention.

A typical known formulation for Tibolone is a 100 mg dosage unit having 2.5 mg of Tibolone contained therein, a relatively small amount (e.g. approximately 1 % by weight) of pharmaceutically acceptable auxiliaries, and a carrier making up the body of the tablet. The carrier typically is composed of 10 % by weight of starch, e.g. potato starch, and 90 % by weight of lactose.

Due to the excellent stability properties of dosage units with a lower amount of active substance than the present commercially available tablets of 2.5 mg active substance, the present invention now makes it also possible to provide for stable dosage units comprising Tibolone in an amount of less than 2.50 mg, preferably 1.25 mg or less, more preferably 0.625 mg or less. At a shelf life of 1.5 years, preferably 2 years these dosage units still comprise less than 5% of OM38 (relative to the amount of Tibolone).

It is another aspect of the present invention to provide dosage units comprising Tibolone in amounts of less than 2.50 mg, preferably 1.25 mg or less, more preferably

0.625 mg or less and comprising at a shelf life of 6 months less than 3 %, preferably 2 % of OM38. The shelf life preferably is extended up to 1 year, preferably 1.5 year, more preferably 2 years.

As used herein shelf life means storage during a specified period under temperature conditions varying from 2-25 °C. Dosage units can be packed e.g. in push-through packs (PTP, blister) and are preferably stored in dark (e.g. enclosed in carton). Alternatively they might also be stored in bottles e.g. high-density polyethylene bottles.

The pharmaceutical dosage units of the present invention will generally take the form of tablets or capsules, but other solid or dry pharmaceutical preparations are included.

Methods for making such dosage units are well known. For example in the standard English language text Gennaro et al., Remington's Pharmaceutical Sciences, (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical Preparations and Their Manufacture), methods of making tablets, capsules and pills and their respective components are described.

Tablets and capsules are prepared of granulates using dry or wet granulation techniques as disclosed in The Theory and Practice of Industrial Pharmacy(Third edition) L. Lachman, H.A.Lieberman and J. L. Kanig (1986) p 1 -99 and 293 - 345.

The aim of granulation is to improve the flowability and compressibility of the powder mixture. Wet granulation forms the granules by binding the powders (a mixture of a diluent and disintegrant) together with an adhesive. The wet granulation technique employs a solution, suspension or slurry containing a binder, which is usually added to the powder mixture; however the binder may be incorporated dry to the powder mix and the liquid may be added by itself. The wet granulation process is performed in mixers/kneaders or fluid bed systems.

Usually an amount of water is incorporated in the basic granulate ranging from 5.5 - 7 %. Preferably the amount of water incorporated is at least 6%.

After granulation the mass is dried to the desired water content using fluid bed dryers, tray dryers, vacuum dryers or other suitable dryers.

To attain a good distribution of the active (Tibolone) over the total mass, the active is premixed with a part of the granulate, sieved using an oscillating sieve, a high speed sieve or other suitable sieving equipment. Next this mixture is mixed with the remaining part of the granulate and a lubricant. This mixture is compressed to tablets, or filled into capsules.

The following examples are illustrative for the invention and should in no way be interpreted as limiting the scope of the invention.

## Examples

### Example 1

A solution of (7α,17α)-3,3-dimethoxy-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one (15 kg) in a mixture of pyridine (630 ml) and ethanol (315 litres) was mixed with a solution of oxalic acid (750 gr) in water (90 litres) and the mixture was stirred for 2 hours at approximately 30 °C. The solution was poured out in a mixture of pyridine (1350 ml) and water (300 litres) and the resulting suspension was filtered. The crystals were washed with a mixture of water and pyridine and dried under vacuum at 40 °C to give (7α,17α)-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one containing 0.6% of the corresponding (7α,17α)-17-hydroxy-7-methyl-19-norpregn-4-en-20-yn-3-one as indicated by HPLC analysis; a stress test at 45 °C (duration 1 month) indicated a 0.4% increase of the latter compound.

### Example 2

A solution of (7α,17α)-3,3-dimethoxy-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one (15 kg) in a mixture of pyridine (630 ml) and ethanol (315 litres) was mixed with a solution of oxalic acid (375 gr) in water (90 litres) and the mixture was stirred for 3 hours at approximately 30 °C. The solution was poured out in a mixture of pyridine (1350 ml) and water (300 litres) and the resulting suspension is filtered. The crystals are washed with a mixture of water and pyridine and allowed to age for 3-6 days at room temperature. Subsequently, the crystals were dried under vacuum at 40 °C to give (7α,17α)-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one containing ≤ 0.1% of the corresponding (7α,17α)-17-hydroxy-7-methyl-19-norpregn-4-en-20-yn-3-one as indicated by HPLC analysis; a stress test at 45 °C (duration 1 week) indicated a < 0.1% increase of the latter compound.

**Example 3**

The preparation as described in example 2 was repeated. (7α,17α)-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one was obtained which contained 0.2 % of the corresponding (7α,17α)-17-hydroxy-7-methyl-19-norpregn-4-en-20-yn-3-one as indicated by HPLC analysis; a stress test at 45 °C (duration 1 week) indicated a 0.1% increase of the latter compound.

**Example 4**

A basic granulate was prepared by granulation of a mixture of lactose (diluent), potato starch (disintegrant) and potato starch mucilage (binder) in a fluid bed granulator. The water content of the granulate varied within 5.5% - 6.5%. After granulation, the basic granulate was passed through a conical high speed sieve. Part of the granulate (10 % w/w) was mixed with Tibolone and ascorbyl palmitate using a tumble blender and then passed through a conical high speed sieve.

The Tibolone premix and the remainder of the basic granulate were mixed in a ribbon blender. Magnesium stearate was added and mixed. The final granulate was compressed into round tablets.

The stability of the active compound (Tibolone) in tablets was determined.

Table 1: Content of decomposition product (Org OM38) in percentage of the declared amount of Tibolone per tablet, in tablets containing a various amount of Tibolone, after storage at 25°C and 60% relative humidity.

| Storage time (months) | Concentration of Tibolone per tablet | | | |
|---|---|---|---|---|
| | 0.46 | 0.96 | 1.92 | 2.5 |
| | Amount of Org OM38 formed during storage (in percentage of the declared amount of tibolone) | | | |
| 0 | 1.2 | 0.8 | 0.5 | 0.4 |
| 6 | 6.5 | 3.5 | 1.8 | 1.6 |
| 12 | 9.5 | 5.1 | 2.7 | 2.2 |
| 18 | 12.2 | 6.1 | 3.3 | 2.7 |

**Example 5**

Tablets of 1.25 mg of Tibolone have been prepared as described in example 4. The tablets were stored at 25°C and 60% relative humidity and the decomposition product (Org OM38) was measured.

Table 2: Content of decomposition product (Org OM38) in percentage of the declared amount of Tibolone per tablet. Stability of three development tablet batches (1.25 mg of Tibolone per 65 mg) was assessed (storage at 25°C and 60% relative humidity).

| Storage time (months) | Batch no 049514001 | 049515001 | 049516001 |
|---|---|---|---|
| | Amount of Org OM38 formed during storage (in percentage of the declared amount of Tibolone) | | |
| 0 | 0.7 | 1.0 | 1.3 |
| 6 | 2.3 | 2.6 | 2.9 |
| 12 | 3.5 | 3.7 | 3.8 |
| 18 | 4.3 | 4.2 | 4.3 |
| 24 | 5.1 | 4.9 | 4.9 |

It can be concluded that the shelf life of tablets containing 1.25 mg of Tibolone per tablet of 65 mg is borderline .

**Example 6**

Tibolone as prepared as in example 2 was used as the active compound to prepare tablets as described in example 4. The amount of Org OM38 formed in several batches during storage was determined.

Table 3: The stability of six tablet batches (1.25 mg of Tibolone per 65 mg) was assessed (storage at 25°C and 60% relative humidity). The amount of water incorporated in the basic granulate was varied from 6.0% to 6.5%.

| | Batch no | | | | | |
|---|---|---|---|---|---|---|
| | TD96.1128 | TD96.1132 | TD96.1133 | 162454001 | 162455001 | 162456001 |
| Storage time (months) | Amount of Org OM38 formed during storage (in percentage of the declared amount of Tibolone) | | | | | |
| 0 | 0.7 | 0.5 | 0.5 | 0.9 | 0.8 | 0.9 |
| 6 | 1.3 | 1.1 | 1.1 | 1.8 | 1.7 | 1.8 |
| 12 | 1.8 | 1.5 | 1.6 | | | |
| 18 | 2.0 | 1.5 | 1.7 | | | |
| Water content of the basic granulate | 6.5 | 6.5 | 6.5 | 6.3 | 6.1 | 6.1 |

## Claims

1. A high purity composition comprising (7α,17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, characterized in that the said composition comprises (7α,17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one in an amount less than 0.5%.
2. The composition according to claim 1 characterized in that the amount of (7α,17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one is 0.25% or less.
3. The composition according to claim 1 characterized in that the amount of (7α,17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one is 0.1% or less.
4. A process for preparing the high purity compositions of claims 1-3 characterized in that crystals of (7α,17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one are allowed to age in the presence of water for at least 24 hours.
5. The process according to claim 4 wherein the aging lasts 3-6 days.
6. The process according to claims 4 or 5 characterized in that the crystals are formed in the last step of the Tibolone synthesis comprising the steps of
   a. reacting (7α,17α)-3,3-dimethoxy-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one in an organic solvent with a weak acidic aqueous solution
   b. pouring out the solution in water which is made slightly alkaline
   c. washing the crystals with water which is made slightly alkaline.
7. A pharmaceutical dosage unit obtainable by admixture of a pharmaceutically suitable solid carrier and the composition according to any one of the claims 1-3.
8. A pharmaceutical dosage unit obtainable by admixture of a pharmaceutically suitable solid carrier and the composition obtainable by the process of claims 4-6.
9. A dosage unit comprising a pharmaceutically suitable solid carrier and (7α,17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one in an amount of less than 2.50 mg and having a shelf life specification comprising less than 5% of (7α,17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one.
10. The dosage unit according to claim 9 characterized in that (7α,17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one is present in an amount of 1.25 mg or less.

11. The dosage unit according to claim 9 characterized in that (7α,17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one is present in an amount of 0.625 mg or less.
12. The dosage unit according to claims 9-11 wherein the shelf life is 1.5 , more preferably 2 years.
13. The dosage unit according to claim 9-11 wherein at a shelf life period of 6 months the amount of (7α,17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one is 3 % or less, more preferably 2% or less.
14. The dosage unit according to claim 13 wherein the shelf life period is 1, preferably 1 ½ year, more preferably 2 years.

EP 1121375

# INTERNATIONAL SEARCH REPORT

Int. .tional Application No
PCT/EP 99/07768

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07J1/00 A61K31/565

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | EP 0 389 035 A (AKZO NV)<br>26 September 1990 (1990-09-26)<br>examples 3,5,8<br>--- | 1-3,7-9,<br>12-14 |
| X | WO 98 47517 A (MORITA RYOICHI ;AKZO NOBEL NV (NL); HAAN DE PIETER (NL); LAMBREGTS)<br>29 October 1998 (1998-10-29)<br>page 2, last paragraph; examples 1-4,6-11<br>--- | 9-14 |
| X | WO 98 39012 A (AKZO NOBEL NV ;ZANDBERG PIETER (NL); MEULEMAN DIRK GERRIT (NL))<br>11 September 1998 (1998-09-11)<br>page 11; example 1; table II<br>--- | 9-14 |
| X | WO 89 09058 A (AKZO NV)<br>5 October 1989 (1989-10-05)<br>example 1<br>---<br>-/-- | 9 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 25 January 2000 | 04/02/2000 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Watchorn, P |

# INTERNATIONAL SEARCH REPORT

Int. .tional Application No
PCT/EP 99/07768

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication,where appropriate. of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | EP 0 707 848 A (AKZO NOBEL NV)<br>24 April 1996 (1996-04-24)<br>example 3 | 9-14 |
| X | EP 0 613 687 A (AKZO NOBEL NV)<br>7 September 1994 (1994-09-07)<br>example 2 | 9 |
| X | EP 0 159 739 A (AKZO NV)<br>30 October 1985 (1985-10-30)<br>example 1 | 9 |
| A | VAN VLIET N P ET AL: "An alternative synthesis of 17.beta.-hydroxy-7.alpha.-methyl-19-nor-17.alpha.-pregn-5(10)-en-20-yn-3-one (Org OD 14)"<br>RECUEIL DES TRAVAUX CHIMIQUES DES PAYS-BAS.,<br>vol. 105, no. 4, April 1986 (1986-04), pages 111-115, XP002099865<br>AMSTERDAM NL<br>page 113, column 1, last paragraph<br>page 115, column 1, paragraph 4 | 1-14 |
| A | DECLERCQ J P ET AL: "Conformational analysis of 3-oxo 5(10)-unsaturated steroids. Single-crystal x-ray structure analysis of 17-hydroxy-7.alpha.-methyl-19-nor-17.alpha.-pregn-5(10)-en-20-yn-3-one (Org OD 14)"<br>RECUEIL DES TRAVAUX CHIMIQUES DES PAYS-BAS.,<br>vol. 103, no. 5, May 1984 (1984-05), pages 145-147, XP002099866<br>AMSTERDAM NL<br>page 146, column 1; table I | 1-14 |
| A | WIELAND P ET AL: "Steroids. CCXI. Synthesis of 7.alpha.-methyl-3-oxo-19-norandrosta-4,9,11-trienes"<br>HELVETICA CHIMICA ACTA,<br>vol. 50, no. 6,<br>21 September 1967 (1967-09-21), pages 1453-1461, XP002099867<br>BASEL CH<br>page 1459, paragraph 1 | 1-14 |
| A | US 3 340 279 A (H. P. DE JONGH ET AL)<br>5 September 1967 (1967-09-05)<br>examples I,II | 1-14 |

-/--

# INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/EP 99/07768

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | FR 1 583 441 A (THE UPJOHN COMPANY) 31 October 1969 (1969-10-31) example 16 | 1-14 |
| A | US 3 475 465 A (WINTER MAX SOLOMON DE ET AL) 28 October 1969 (1969-10-28) example II | 1-14 |
| A | US 3 432 528 A (ANNER GEORG ET AL) 11 March 1969 (1969-03-11) example 3 | 1-14 |
| A | US 3 576 828 A (ANNER GEORG ET AL) 27 April 1971 (1971-04-27) example 9 | 1-14 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ional Application No
PCT/EP 99/07768

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| EP 0389035 A | 26-09-1990 | AT 98490 T | 15-01-1994 |
| | | AU 625083 B | 02-07-1992 |
| | | AU 5139490 A | 20-09-1990 |
| | | CA 2011452 A | 18-09-1990 |
| | | DE 69005165 D | 27-01-1994 |
| | | DE 69005165 T | 05-05-1994 |
| | | DK 389035 T | 14-02-1994 |
| | | ES 2062292 T | 16-12-1994 |
| | | FI 94865 B | 31-07-1995 |
| | | HK 1002019 A | 24-07-1998 |
| | | IE 63051 B | 22-03-1995 |
| | | JP 3047195 A | 28-02-1991 |
| | | MX 9203787 A | 01-07-1992 |
| | | NZ 232946 A | 27-08-1991 |
| | | PT 93488 A,B | 07-11-1990 |
| | | US 5037817 A | 06-08-1991 |
| WO 9847517 A | 29-10-1998 | AU 8014698 A | 13-11-1998 |
| | | JP 10316573 A | 02-12-1998 |
| | | NO 995127 A | 21-10-1999 |
| | | ZA 9803169 A | 20-10-1998 |
| WO 9839012 A | 11-09-1998 | AU 6728498 A | 22-09-1998 |
| | | ZA 9801731 A | 07-09-1998 |
| WO 8909058 A | 05-10-1989 | AU 3435989 A | 16-10-1989 |
| | | DK 224690 A | 18-09-1990 |
| | | EP 0406279 A | 09-01-1991 |
| | | JP 3503414 T | 01-08-1991 |
| EP 0707848 A | 24-04-1996 | AU 688581 B | 12-03-1998 |
| | | AU 3426795 A | 02-05-1996 |
| | | BR 9504400 A | 27-05-1997 |
| | | CA 2159419 A | 18-04-1996 |
| | | CN 1130064 A | 04-09-1996 |
| | | FI 954905 A | 18-04-1996 |
| | | HU 75247 A | 28-05-1997 |
| | | IL 115445 A | 17-08-1999 |
| | | JP 8268914 A | 15-10-1996 |
| | | TR 960302 A | 21-06-1996 |
| EP 0613687 A | 07-09-1994 | AT 180669 T | 15-06-1999 |
| | | AU 671706 B | 05-09-1996 |
| | | AU 5754294 A | 08-09-1994 |
| | | CA 2116829 A | 06-09-1994 |
| | | DE 69418744 D | 08-07-1999 |
| | | DE 69418744 T | 11-11-1999 |
| | | ES 2134313 T | 01-10-1999 |
| | | JP 7002673 A | 06-01-1995 |
| | | NO 940777 A | 06-09-1994 |
| | | NZ 260017 A | 24-06-1997 |
| | | US 5512556 A | 30-04-1996 |
| | | ZA 9401464 A | 27-09-1994 |
| EP 0159739 A | 30-10-1985 | AT 42895 T | 15-05-1989 |
| | | JP 1829698 C | 15-03-1994 |
| | | JP 60209599 A | 22-10-1985 |
| | | MX 9203811 A | 01-07-1992 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte .ional Application No
PCT/EP 99/07768

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| EP 0159739 A | | US 4701450 A | 20-10-1987 |
| US 3340279 A | 05-09-1967 | NL 6406797 A | 17-12-1965 |
| | | BE 665514 A | |
| | | CH 517725 A | 15-01-1972 |
| | | DE 1543273 A | 07-08-1969 |
| | | DK 114553 B | 14-07-1969 |
| | | FR 1594513 A | 08-06-1970 |
| | | GB 1104462 A | |
| | | SE 336788 B | 19-07-1971 |
| FR 1583441 A | 31-10-1969 | BE 712229 A | 16-09-1968 |
| | | CH 516545 A | 15-12-1971 |
| | | DE 1668818 A | 30-09-1971 |
| | | GB 1206872 A | 30-09-1970 |
| | | GB 1206873 A | 30-09-1970 |
| | | GB 1206874 A | 30-09-1970 |
| | | NL 6803328 A | 16-09-1968 |
| | | US 3515719 A | 02-06-1970 |
| US 3475465 A | 28-10-1969 | NL 6608779 A | 27-12-1967 |
| | | BE 700390 A | 27-12-1967 |
| | | CH 537913 A | 31-07-1973 |
| | | DE 1618747 A | 25-02-1971 |
| | | DK 115989 B | 01-12-1969 |
| | | FR 1527563 A | 06-11-1968 |
| | | GB 1177845 A | 14-01-1970 |
| US 3432528 A | 11-03-1969 | BE 684851 A | 30-01-1967 |
| | | BE 684852 A | 30-01-1967 |
| | | CH 488682 A | 15-04-1970 |
| | | CH 509996 A | 15-07-1971 |
| | | CH 519488 A | 29-02-1972 |
| | | CH 525873 A | 31-07-1972 |
| | | DE 1568308 A | 05-02-1970 |
| | | DE 1568306 A | 12-03-1970 |
| | | DE 1568307 A | 05-02-1970 |
| | | FR 5260 M | 24-07-1967 |
| | | FR 6350 M | 07-10-1968 |
| | | FR 1491586 A | 30-11-1967 |
| | | FR 1491587 A | 30-11-1967 |
| | | FR 1491588 A | 30-11-1967 |
| | | GB 1158331 A | 16-07-1969 |
| | | GB 1158332 A | 16-07-1969 |
| | | NL 6610741 A,B | 31-01-1967 |
| | | NL 6610742 A,B | 31-01-1967 |
| | | NL 6610743 A,B | 31-01-1967 |
| | | NL 7607401 A | 29-10-1976 |
| | | US 3576828 A | 27-04-1971 |
| | | ES 329609 A | 01-03-1968 |
| | | CS 153439 B | 25-02-1974 |
| US 3576828 A | 27-04-1971 | BE 684851 A | 30-01-1967 |
| | | BE 684852 A | 30-01-1967 |
| | | CH 488682 A | 15-04-1970 |
| | | CH 509996 A | 15-07-1971 |
| | | CH 519488 A | 29-02-1972 |
| | | CH 525873 A | 31-07-1972 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. ional Application No
PCT/EP 99/07768

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US 3576828 A | | DE 1568308 A | 05-02-1970 |
| | | DE 1568306 A | 12-03-1970 |
| | | DE 1568307 A | 05-02-1970 |
| | | FR 5260 M | 24-07-1967 |
| | | FR 6350 M | 07-10-1968 |
| | | FR 1491586 A | 30-11-1967 |
| | | FR 1491587 A | 30-11-1967 |
| | | FR 1491588 A | 30-11-1967 |
| | | GB 1158331 A | 16-07-1969 |
| | | GB 1158332 A | 16-07-1969 |
| | | NL 6610741 A,B | 31-01-1967 |
| | | NL 6610742 A,B | 31-01-1967 |
| | | NL 6610743 A,B | 31-01-1967 |
| | | NL 7607401 A | 29-10-1976 |
| | | US 3432528 A | 11-03-1969 |
| | | ES 329609 A | 01-03-1968 |
| | | CS 153439 B | 25-02-1974 |